

IL-17 and IL-10 as potential biomarkers for diagnosing periodontitis patients: A Review

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Abstract

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Background: Evaluation methods for periodontal disorders are continually being refined to yield more precise, reliable, and time-efficient findings. Radiographic reports and clinical assessments of periodontal tissues, which served as the basis for earlier trends, were used to identify disorders affecting the tooth-supporting structures. As traditional approaches have become more apparent gradually over time, new methods emerged, some of which have been empirically validated. One example is the detection and measurement of biomarkers in bodily fluids. One of the most pressing issues in periodontal field nowadays is the search for an idealized periodontal diagnostic/prognostic biomarker that can both identify diseased areas and track the therapeutic success of periodontal treatment. Both IL-17 and IL-10 have shown connection to periodontitis that could encourage using them as diagnostic tools.

Objective: To provide a review of the role and association of the above biomarkers to periodontitis.

Patients and Methods: A systematic research of Google scholar, Scopus, PubMed Central, research gate was conducted using keywords such as diagnosis, periodontitis, IL-17, IL-10, biomarkers, Saliva and gingival crevicular fluid (GCF).

Results: out of 58 records which resulted from the initial search only 14 were included which used roles, associations, and diagnosis as their outcomes.

Conclusion: Evidence from the selected records suggests that the above stated biomarkers might be able to discriminate periodontitis from health, monitoring disease progression and post treatment outcome, but actual clinical application needs much further research.

Keywords: periodontitis, Diagnosis, IL-17, IL-10

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Introduction

Periodontitis is a gradual breakdown of the structures supporting the teeth caused by a chronic, multifaceted inflammatory illness linked to plaque-biofilms dysbiosis. The basic characteristics of this condition are the loss of support from periodontal tissue, as evidenced by clinical attachment loss (CAL) and alveolar bone loss that is

radiographically measured, the presence of periodontal pocketing, and the bleeding of the gingiva [1].

Knowing how immune systems and inflammatory responses are regulated is necessary for comprehending the pathophysiology of complex illnesses like periodontitis. It has long been established that

periodontitis has a multi-microbial origin. Tissue deterioration of periodontal supporting tissues is caused not only by dental dysbiosis but also by host immune inflammatory dysregulation [2]. Being part of the immune system, cytokines play significant role in periodontal disease pathogenesis, they are classified as proteins with a low molecular weight that have a role in the onset and progression of inflammation by controlling the intensity and length of the reaction [3][4].

Overall results from several studies show that the imbalance between pro and anti-inflammatory cytokines harms periodontal tissues and prevents inflammation from subsiding [5,6].

Many inflammatory conditions have had their cytokine concentrations compared between healthy and diseased states, and periodontitis is no exception.

In one way or another, periodontal disorders have impacted practically all areas of dentistry. First and foremost, periodontal disease affects people differently. Apart from the inaccessible regions and portions of the oral cavity, clinical symptoms might occasionally be undetectable because of poor sight and the inability to thoroughly evaluate those spots.

Hence, periodontitis detection requirements are still not reached by the conventional clinical diagnostic techniques (such as examination, palpation, periodontal probing, and radiography) [7] because periodontitis is still only recognized after oral tissue and bone loss has taken place.

That's why identifying biomarkers for early detection is unquestionably necessary in order to find novel treatment options and

understand the causes and susceptibility of disease.

It's noteworthy to mention that during any periodontal infection, parts of defense system of the host and pro-inflammatory mediators are elevated and incorporated locally as well as in oral fluid as saliva and gingival crevicular fluid (GCF) [8].

In this review the aim was to evaluate the current literature regarding the role, association and diagnostic value of IL-17 and IL-10 in only GCF and saliva excluding plasma, serum, gingival tissue biopsies and plaque samples.

Interleukin- 17

Interleukin-17 is an emerging pro-inflammatory cytokine that has both beneficial and harmful effects. [9,10] .It is a hallmark cytokine of Th17 cells and serves as a link between the innate and adaptive immunity at the mucosal barriers[11]. Emerging as potentially essential participants in the pathophysiology of periodontitis, interleukin-17 (IL-17) and IL-17-producing lymphocytes and innate immune cells are of special interest.

Despite having a major role, whether this role is protective or destructive is still a matter of controversy, [12] and this is due to the considerable variation in the way IL-17 is expressed in periodontitis from various reports, it is suggested to be engaged in both the pro-inflammatory and antimicrobial immune defense mechanisms [13]. In the latter case, it has been demonstrated that IL-17 induces the generation of antimicrobial peptides and mediates defense against infections extracellularly [13,14] [15] On the destructive side however, it promotes periodontal tissue destruction via: first,

mediating neutrophil recruitment to periodontal lesions and subsequent activation of them to engage in local inflammatory responses. [16] Second, to intensify the inflammatory response, it causes fibroblasts and epithelial cells to release several pro-inflammatory molecules such as interleukins, macrophage colony-stimulating factor, and cell adhesion molecules [17] and most importantly, In addition to increasing RANKL-mediated osteoclast formation, IL-17 also induces osteoclast differentiation, making it an important component in the control of bone homeostasis [18].

In principle, therefore, IL-17 can have both beneficial and detrimental effects, making it a potential double-edged sword in the fight against a bacterially initiated illness like periodontitis which is caused by bacteria yet results in tissue damage due to the host's immune response [19].

Interleukin-10

IL-10 is one of the most effective anti-inflammatory cytokines that inhibits immune cell proliferation and inflammation [20].

In other words, it is a cytokine involved in immune regulation preventing LPS- or IFN- γ -stimulated immune cells from releasing a variety of pro-inflammatory mediators [21].

IL-10 has long been thought to be an inhibitor of cytokine production, but new evidence supports its role in immune regulation, both IL-10 deficiencies and excesses were linked to autoimmune diseases and inflammatory disorders. Generally speaking, IL-10 shifts the Th1/Th2 balance in favor of cytokine type 2 pattern [22] while also reducing the manufacture of Th1 cytokines, which in turn lowers the production of proinflammatory cytokines and

chemokines such as IL-1, IL-6, and TNF- α . [23,24,25].

In periodontitis IL-10 protects against the disease by preventing the production of pro-inflammatory cytokines and taming an overactive IL-17-mediated inflammatory response [11] and, through the induction of tissue inhibitors of metalloproteinases and the inhibitor of osteoclastogenesis osteoprotegerin and thus, attenuating periodontal tissue destruction [26]. Knowing that IL-10 prevents bone loss, using it as a treatment for periodontitis and other bone loss illnesses might be successful [27].

According to several reports, IL-10 plays a significant role in human periodontitis, where low levels of this cytokine are linked to disease severity [28,29], accelerating the development of the condition from gingivitis to periodontitis [30]. Therefore, this cytokine may be of fundamental importance in the control of periodontal disease.

Biomarkers

According to the National Institutes of Health (NIH), a definition of biomarker would be "an objectively measured and analyzed trait that serves as an indication of normal and pathogenic processes, or pharmacological reactions to a treatment intervention" [31].

Identifying and quantifying biomarkers found in physiological fluids are important in clinical and research practices for monitoring pathological illness status, hereditary susceptibilities, and physiological responses to drugs or environmental stimuli [32]. Therefore, biomarkers have shown effective in the prevention, diagnosis, and prognosis of a variety of diseases, as well as in tracking the progression of pathological situations [33].

According to the available literature about the clinical parameters having limitations in determining the current disease status, [34] this made it particularly appealing to look for biomarkers that may quickly, accurately, and easily discriminate destructive periodontal disease from gingival inflammation and health. Identifying "at risk" people before periodontal tissue damage starts, determining disease activity and progression, and expanding our understanding of this complicated illness in order to uncover novel treatment targets are the three major goals driving research into periodontitis biomarkers [35].

Periodontal disease ideal biomarkers should be able to 1) detect the illness's presence, 2) represent its severity, 3) track the healing process, and 4) predict the disease's future. [36] More specifically, diagnostic biomarkers must have a diagnostics methodology that is highly repeatable, with established accuracy, sensitivity, specificity, false positive rate, false negative rate, and diagnostic range properly reported in the diagnostic material [37].

Saliva and GCF as biological fluids for diagnosing periodontitis:As oral fluids include indicators unique to periodontal disease, they are rightfully regarded as a reflection of periodontal health and as a vehicle for the dissemination of clinically useful information [38].

Various fluid vehicles are available for monitoring the activity of periodontal disease like saliva, serum and GCF, but due to their simplicity of collection and abundance in locally and systemically generated indicators of periodontal disease, saliva and GCF have

tremendous promise for the evaluation of patient-specific biomarkers in the diagnosis of periodontitis and other systemic diseases[39].

Saliva is a known biological fluid for diagnostic use, and collecting of samples is possible even for those without dental training,[40] it provides solutions to some of the difficulties inherited in GCF sampling as saliva is more accessible, plentiful, and may be sampled in considerably greater volume than GCF without the requirement for clinical facilities, and accurate sampling does not necessitate complicated expertise, it contains components that are indicative of inflammation at all periodontal sites (whole mouth) rather than just those that are actively diseased[41,35].

Most importantly, saliva can be used to detect tissue-destructive mediators such cytokines, chemokines, and cellular destructive enzymes, as well as chemicals generated as a direct result of tissue injury during the periodontal pathogenesis [39].

Talking about GCF, It's one of the most site-specific fluids, elucidating the area's unique anatomy to aid in the diagnosis, treatment, and management of a wide range of disorders [42].

It is dependable like other oral fluids but, in contrast to saliva, it is a very fragile specimen that protects the junctional epithelium (JE) from damage, [43], It can reflect the condition of the periodontal tissues over time and be used to measure biomarkers of inflammatory origin, tissue remodeling, and bone metabolism because it is a serum transudate in health and tissue exudate in disease. It is enriched with biological

signatures from both inflammatory and immune reaction to the plaque biofilm [40].

Point Of Care (POC)

Point-of-care testing (POCT) is laboratory clinical testing done away from the main lab, often closer to the patient, and occasionally right at the patient's bedside [44].

Inspection, palpation, periodontal probing, and radiography are the most documented clinical diagnosis methods, yet they fall short when it comes to fully satisfy the detection of periodontal disease. As a result, there is a pressing need to provide simple, inexpensive, and efficient techniques of diagnosing and tracking periodontitis [7].

In order to be considered as effective diagnostic markers that might be employed chairside or in a home use device, the concepts of these novel diagnostic procedures heavily rely on the identification of the indicators of disease activity [38]. The characteristics and detection principles of POCT devices have recently been improved by merging several nanomaterials and platforms, making them ideal for high-frequency periodontitis diagnosis at POC. Technology like LOC (lab on a chip) and micro-fluidic devices have been a major source of optimism for controlling oral fluids like GCF and saliva. Moreover, they establish the patient's risk profile, current disease activity and therapeutic response. This information aids in clinical decision-making and the monitoring of the episodic character of periodontitis [45].

Patients and Methods

A systematic search was performed using Google scholar, PubMed Central, Scopus, database from 2011 to 2022 with the following search strategies: diagnosis,

periodontitis, IL-17, IL-1-0, biomarkers or markers, saliva and GCF.

The search was limited to English language, studies that fulfil the next criteria were included: (a) adult systemically healthy participants, (b) assessment of salivary and GCF biomarker's levels, (c) comparative studies which measured IL-17 and IL-10 concentration both in periodontitis and in health (d) follow up studies which monitored biomarker's level before and after periodontal therapy.

Exclusion criteria were as follows: studies that used tissue samples like gingival tissues or plaque as their biological media, study participants with risk factors like smoking and underlying systemic diseases.

Results

The initial search resulted in 58 articles. After elimination of duplications, titles, abstracts and outcome, the selected papers were further screened and only 14 papers using GCF and/or saliva were reviewed and evaluated in accordance with the inclusion and exclusion criteria.

Out of 14 papers, IL-17 had a greater portion of the search results with 9 articles than IL-10 which had only 6, this is because IL-17 has been the focus of periodontal biomarker research in the recent years due to its controversial role in periodontal disease pathogenesis, and moreover, most available literature regarding IL-10 either used the genetic component of this marker or measured IL-10 levels in biological fluids other than saliva or GCF such as serum or plasma. The included studies used roles, associations, and diagnostic potential of the selected biomarkers as their outcome, Table (1) summarizes the results of this search.

Table (1): Association of (IL-17, IL-10) with periodontitis

Author, year	Aim	Sample (n)	Biomarkers	Conclusion, Outcome
Nair et al. (2022) [46]	explore the role of three cytokines, interleukin (IL)-17, 18 and 21, by measuring their levels in the gingival crevicular fluid (GCF)	90 (30 healthy, 30 gingivitis, 30 periodontitis)	IL-17, IL-18, IL-21	Increases in GCF levels of IL-17, IL-18, and IL-21 which might be regarded as indicators of periodontal tissue damage and they linked strongly with the severity of the disease.
Vahabi et al. (2020) [47]	Compare salivary concentrations of (IL-17) and (IL-18) in patients with periodontitis and healthy individuals.	40 (20 periodontitis, 20 healthy)	IL-18 IL-17	When compared to controls, salivary levels of IL-17 were considerably lower while IL-18 were greater in individuals with periodontitis.
Inönü et al. (2020) [48]	Evaluate levels of Salivary Del-1, IL-17, and LFA-1 levels in periodontal health and disease.	180 (45 periodontally healthy, 45 gingivitis, 90 periodontitis)	Del-1, IL-17, and LFA-1	Increased levels of IL-17 were found in periodontitis, and these levels may serve as helpful indicators for determining the clinical health and disease state of periodontitis patients.
Taiete et al. (2019) [49]	Identify the predictive value of immunological pattern on clinical response to therapy	24 periodontitis (12 treated with SRP, 12 with SRP+ antimicrobial therapy)	IL-10	IL-10 levels act as predictors of clinical response to periodontitis
Fahmi et al. (2019) [50]	determine the difference in the salivary levels of IL-17 between periodontally healthy and periodontitis subjects	48 (24 patients with periodontitis and 24 healthy)	IL-17	The results are highly and significantly increased to differentiate periodontal health from periodontitis.
Batool et al. (2018) [51]	Determine levels of salivary IL-6 and IL-17 in patients with calculus associated periodontitis.	82 (41 healthy and 41 calculus associated periodontitis (CP))	IL-17 IL-16	Significant association between the salivary levels of the selected biomarkers and periodontitis
Öngöz et al. (2017) [53]	explore fluctuations in the levels of TNF- α , IL-32 and IL-10, in both saliva and gingival crevicular fluid	54 (27 periodontitis, 27 healthy)	IL-10, IL-32, TNF- α	In the periodontitis group, saliva and GCF levels of IL-10 were considerably lower at baseline than they were after treatment.
Yang et al. (2016) [52]	Level of salivary interleukin-17 1- and 3-months post OHI and SRP	92 (45 periodontitis, 47 control)	IL-17	In contrast to the baseline, IL-17 levels dropped considerably after therapy.
Zhang et al. (2016) [54]	To compare biomarkers' levels in GCF in different tooth sites of subjects with healthy periodontium and periodontitis, to evaluate the value of these markers for diagnosing type and	40 (30 periodontitis, 10 healthy controls)	IL-10, IL-6, tumor necrosis factor (TNF- α), C-reactive protein (CRP)	The estimate of periodontitis activity and overall screening of periodontitis patients may be facilitated by the detection of biomarker levels in GCF.

	activity of periodontitis			
Feno et al. (2014) [55]	determine whether variations in GCF levels of interleukin-10 have a role in preventing progression of gingivitis to periodontitis	91 (30 healthy, 31 gingivitis, 30 periodontitis)	IL-10	Gingivitis group had the highest level of IL-10 and lowest for control group while for periodontitis was found to be intermediate between them.
Awang et al. (2014) [56]	determine clinical associations between IL-17 family cytokines and periodontitis	174 (97 with periodontitis and 77 healthy)	IL-17	saliva and GCF IL-17A levels correlated positively with all clinical parameters (pocket probing depth, bleeding on probing, clinical attachment loss)
Prakasam et al. (2014) [57]	Monitor Changes in salivary cytokines levels after non-surgical periodontal therapy (SRP)	32 (18 periodontitis, 18 healthy)	IL- 10, IL-17	No significant change in salivary IL-17 levels post SRP, while IL-10 levels were significantly higher at 6 weeks post-SRP.
Archana et al. (2014) [58]	Evaluation of salivary IL-10 levels and its relationship to its circulatory levels	Total 30 patients (Periodontally health & disease)	IL-10	Significant decrease of salivary IL-10 levels in periodontal disease when compared to health.
Özçaka et al. (2011) [59]	Investigate the difference in salivary concentrations of interleukin IL-17, IL-18 in periodontitis compared with clinically healthy subjects.	43 (22 chronic periodontitis, 21 healthy)	IL-17 IL-18	Significantly lower salivary IL-17 concentrations and higher IL-18 concentrations in the periodontitis subjects compared to healthy subjects

Conclusions

In conclusion, this review summarizes the importance of analyzing constituents of saliva and GCF as diagnostic/prognostic means, markers of current disease activity as wells as post therapy follow up. Aspects that the traditional clinical methods fail to provide. Results and outcomes of the selected data clearly demonstrate the link of IL-17 and IL-10 to periodontitis and thus, with their diagnostic, prognostic significance could act as a valuable tool in the combat of periodontal disease. However, one of the main limitations of this review is the lack of a

unified periodontal classification system since published literature on the review subject according the 2017 classification for periodontal and peri- implant diseases and conditions [60] are limited. And so, the majority of the included studies adopted the 1999 classification system for periodontal diseases and conditions [61] in addition to the difference in study designs, settings and interpretation of the results.

Recommendations

Monitoring the biomarkers longitudinally, (from health to the full-blown disease state) by salivary genomics, proteomics, and other

state-of-the-art diagnostic techniques to follow changes in biomarker's levels through the various stages of the disease.

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Ethical clearance: This report was conducted in accordance with the declaration of Helsinki after being approved by the ethical committee in Baghdad college of dentistry.

Conflict of interest: Nil

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الانترلوكين-١٠ و الانترلوكين-١٧ كمؤشرات حيوية محتملة لتشخيص مرضى التهاب اللثة: مراجعة

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المخلص

خلفية الدراسة: تتطور المنهجيات المطبقة لتقييم أمراض اللثة باستمرار لتقديم نتائج سريعة وواقعية ومثبتة علمياً. اتبعت الاتجاهات في الماضي تقييماً سريرياً لأنسجة اللثة وتقارير قائمة على التصوير الشعاعي شكلت الأساس للكشف عن الأمراض التي تنطوي على الهياكل الداعمة للأسنان. نظراً لأن حدود الاستراتيجيات التقليدية وقيودها أصبحت واضحة بمرور الوقت ، فقد تطورت مجموعة متنوعة من التقنيات وتبريرها تجريبياً مثل تحديد المؤشرات الحيوية الموجودة في السوائل البيولوجية وتحديد الكمي والتي تكون مفيدة لتقييم حالة الحالات المرضية والحساسيات الجينية واستجابات الجسم للعقاقير أو العوامل البيئية. اليوم ، في مجال علاج دواعم السن ، يتمثل أحد التحديات الرئيسية في اكتشاف علامة بيولوجية تشخيصية تكهنه مثالية للثة والتي يجب أن تكون قادرة على اكتشاف المواقع المريضة ومراقبة استجابة المرض لعلاج اللثة. أظهر كل من IL-17 و IL-10 صلة بالتهاب دواعم السن التي يمكن أن تشجع على استخدامها كأدوات تشخيصية.

اهداف الدراسة: لتقديم مراجعة لدور وترايط المؤشرات الحيوية المذكورة أعلاه مع التهاب اللثة.

المرضى والطرائق: تم إجراء بحث منهجي لباحث Google scholar ، Scopus ، PubMed Central ، وبوابة البحث باستخدام كلمات رئيسية مثل التشخيص ، والتهاب اللثة ، و IL-17 ، و IL-10 ، والعلامات الحيوية ، واللغاب ، والسائل الجروحي اللثوي (GCF).

النتائج: من أصل ٥٨ سجلاً نتجت عن البحث الأولي ، تم تضمين ١٤ سجلاً فقط والتي استخدمت الأدوار و الارتباطات و التشخيص كنتائج لها.

الاستنتاجات: تشير الدلائل من السجلات المختارة إلى أن المؤشرات الحيوية المذكورة أعلاه قد تكون قادرة على تمييز التهاب دواعم السن عن الصحة ، ومراقبة تطور المرض ونتائج ما بعد العلاج ، لكن التطبيق السريري الفعلي يحتاج إلى مزيد من البحث.

الكلمات المفتاحية: التهاب اللثة، الانترلوكين-١٠، الانترلوكين-١٧، التشخيص

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